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van IJzendoorn, Sven C. D.

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Sven C. D. van IJzendoorn

Department of Cell Biology, section Membrane Cell Biology, University Medical Center Groningen, University of Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen, The Netherlands

e-mail: s.c.d.van.ijzendoorn@med.umcg.nl

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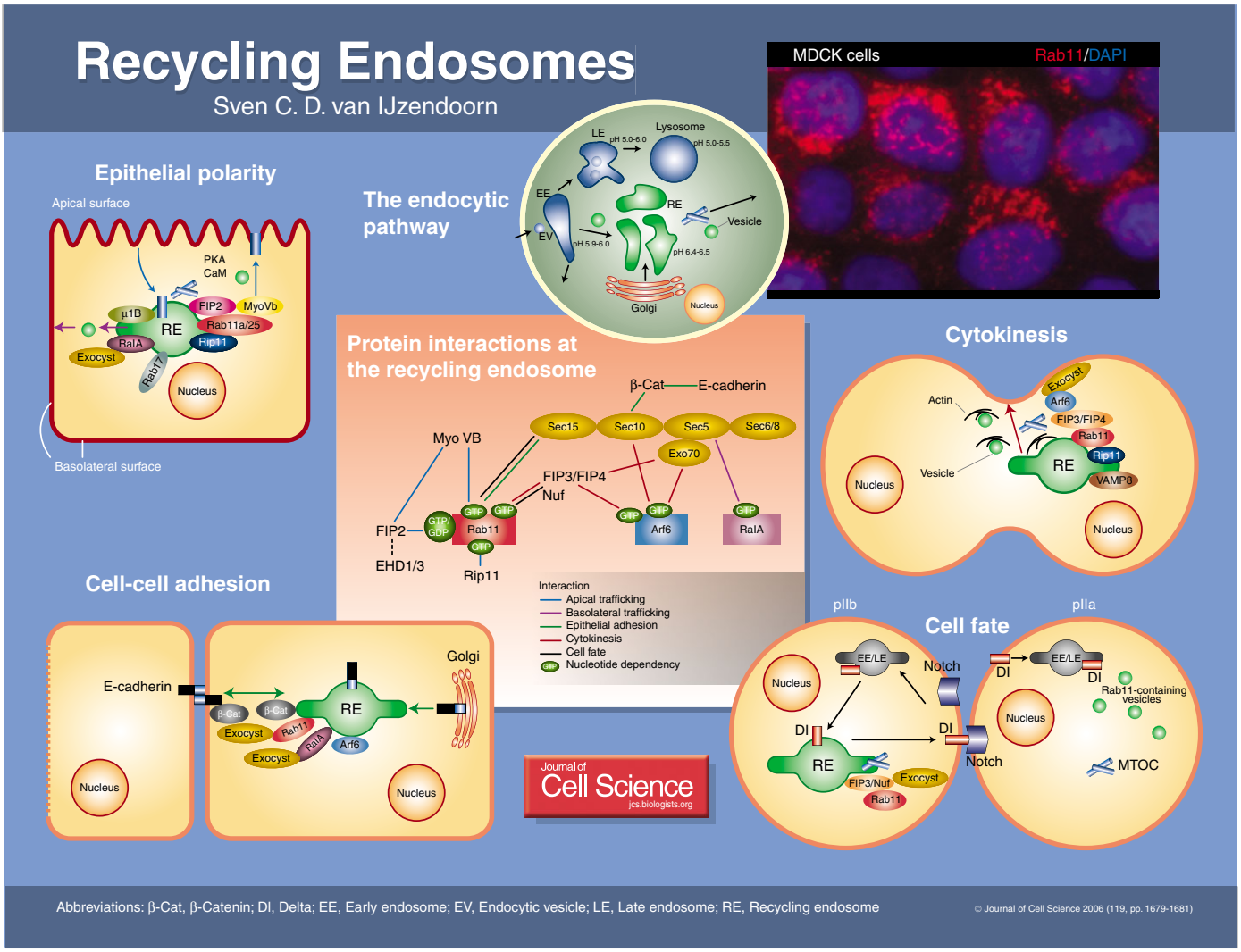
The endocytic and exocytic system is important for cells to communicate with their surroundings. For instance, endocytosis allows the regulated internalisation of receptors (which can be ligand bound or not) into peripheral early endosomes and can thus modulate responses to external stimuli. Internalised molecules can be degraded after entering the late-endosomal/lysosomal pathway or be recycled to the cell surface (Maxfield and McGraw, 2004). Recycling to the cell surface can occur directly from peripheral early endosomes. However, many cells display a distinct subpopulation of endosomes that have a slightly higher pH of ~6.4 and also recycle membrane components. These are typically located deeper in the cell and centered around the microtubule-organising centre (MTOC) (Perret et al., 2005). These so-called recycling endosomes (REs) display a heterogeneous tubular-vesicular morphology, which suggests dynamic and intense trafficking activity, and connect the endocytic pathway to the exocytic pathway (Ang et al., 2004; Lock and Stow, 2005; Murray et al., 2005).

The most prominent RE marker to date is the small GTPase Rab11. Studies of the function of Rab11 and the proteins with which it interacts in various experimental systems and organisms suggest that cells use REs for the delivery of membranes to regions of their surface that are subject to dynamic reorganisation, probably through regulated interactions with the exocyst, a multiprotein complex containing the Sec5, Sec6, Sec8, Sec10, Sec15 and Exo70 proteins that is thought to recruit material to areas of membrane growth. Consequently, REs are implicated in the regulation of a variety of cellular processes that depend on such trafficking. Several of these are highlighted in the poster and discussed briefly below.

Epithelial cell-cell adhesion

E-cadherin-mediated cell-cell adhesion controls epithelial cell polarisation,



(See poster insert)

morphogenesis, and the generation and maintenance of a protective epithelial barrier. Epithelial cell-cell adherens junctions are dynamic and, accordingly, E-cadherin is subject to internalisation and recycling. Overexpression of wild-type Rab11 or a GTP-locked Rab11 mutant in epithelial cells causes the accumulation of newly synthesized E-cadherin in enlarged REs, impairs trafficking of E-cadherin to the lateral cell surface and results in a morphological transformation of epithelial cells (Lock and Stow, 2005). Similarly, overexpression of a GTP-locked Arf6 mutant causes loss of cell-cell adhesion concomitant with accumulation of E-cadherin in REs (Palacios et al., 2001).

Polarised targeting of vesicles requires their recognition by the target membrane, a step that involves the exocyst complex. RalA, another small GTPase involved in cellular transformation, localises to REs and stimulates trafficking of E-cadherin to the cell surface through interactions with Sec5 and other exocyst components (Shipitsin and Feig, 2004). In *sec5*, *sec6* and *sec15* mutant *Drosophila* nota epithelial cells, E-cadherin accumulates in enlarged Rab11-positive REs (Langevin et al., 2005). The exocyst components Sec15 and Sec5 interact with GTP-bound Rab11 (Zhang et al., 2004; Beronja et al., 2005) and Sec10 interacts with *Drosophila* β-catenin (Armadillo). Rab11 and the exocyst at the RE may jointly regulate trafficking of E-cadherin to the epithelial cell surface where β-catenin is localised (Langevin et al., 2005). In *Drosophila* wing epithelial cells, Sec5 and Rab11 are required to deliver cadherin to junctions, and this requirement is acute during hexagonal repacking (Classen et al., 2005). The RE thus appears to be an important compartment in the dynamic control of cell adhesion in epithelia and processes that require this.

Epithelial polarity

Polarised epithelial cells display apical and basolateral surface domains. Accordingly, distinct apical and basolateral early endosomes have been described. Downstream of these early endosomes, internalised apical and basolateral proteins and lipids meet in late-endosomal structures or in a common RE (also called the subapical compartment or SAC) (van IJzendoorn and Hoekstra, 1999), which is typically located near the centrosome in the apical cytoplasm. REs govern the polarised distribution of proteins and lipids from the endocytic pathway (reviewed by van IJzendoorn and Hoekstra, 1999) and the biosynthetic pathway (Ang et al., 2004; Lock and Stow, 2005).

Polarised recycling from REs depends on actin and Rab17. Rab25 and Rab11a also localise to REs but are spatially segregated from Rab11b and basolaterally recycling proteins – they probably reside in a RE subcompartment or a subdomain oriented towards the apical surface (referred to as the apical RE) (Hoekstra et al., 2004). At the apical RE, Rab11a can interact directly with Rip11, myosin Vb and/or FIP2 (for Rab11a Family of Interacting Proteins); myosin Vb binds to FIP2. RNAi-mediated downregulation, or expression of mutated forms, of Rab25, Rab11a, myosin Vb, Rip11 or FIP2 impairs signal-stimulated recruitment of recycling proteins from the apical RE to the apical surface of kidney, gastric and hepatic epithelial cells (Casanova et al., 1999; Duman et al., 1999; Wang et al., 2000; Lapierre et al., 2001; Hales et al., 2002) and inhibits the biogenesis of the apical, bile canalicular surface in hepatocytes (Wakabayashi et al., 2005). Recycling from the RE to the apical surface and apical surface biogenesis in hepatocytes are also calmodulin- and microtubule-dependent and controlled by interplay between interleukin-6-family cytokines, protein kinase A signalling, sphingoid base turnover, and $p27^{Kip1}$/Cdk2-regulated events at the centrosome (van IJzendoorn et al., 2004a; van IJzendoorn et al., 2004b).

Besides regulating apical trafficking, REs may also control the basolateral delivery of newly synthesised proteins via RalA and the epithelial-specific adaptor protein subunit μ1B in cooperation with the exocyst complex (Fölsch, 2005). REs therefore appear to be heavily involved in the polarised delivery of recycling and newly synthesised proteins and the consequent development of asymmetric cell surface domains.

Cytokinesis

Rab11a remains associated with REs during cell cycle progression, which may allow rapid redistribution of cell surface components following mitosis (Hobdy-Henderson et al., 2003). During *Drosophila* embryogenesis, membrane trafficking through Rab11-positive REs is required for cellularisation (Pelissier et al., 2003). This requires coordinated remodelling of actin filaments and addition of new membrane to form the cleavage furrow. In addition to regulating membrane supply, REs also regulate actin remodelling during early *Drosophila* furrow formation through Rab11 and Nuclear fallout (Nuf) (Riggs et al., 2003); the latter also localises to centrosomes. Nuf is a *Drosophila* orthologue of arfophilin, an Arf–GTPase-binding protein that is identical to the Rab11-binding protein eferin/FIP3 (Hickson et al., 2003). FIP3/Nuf localises to the cleavage furrow during cytokinesis (Horgan et al., 2004), and the Rab11-FIP3/Nuf complex regulates targeting of REs to the cleavage furrow during late cytokinesis (Wilson et al., 2005). Moreover, FIP3 and FIP4 interact with Arf6 at the RE and the exocyst component Exo70 at the furrow to control membrane traffic during cytokinesis (Fielding et al., 2005), although the exact role of FIP4 in this is not clear. Arf6 also interacts with Sec10 and Sec5 (Prigent et al., 2003), which are intimately involved in RE dynamics during cell-cell adhesion (see above). Cytokinesis requires membrane fusion mediated by the SNARE protein VAMP8 (Low et al., 2003), which colocalises with Rab11a at the RE and is regulated by Rip11 (Prekeris et al., 2000). FIP3/Nuf, FIP4, Rab11 and Arf6, the exocyst complex and VAMP8 are all essential for the completion of cell division.

Cell fate specification

Asymmetric division of sensory organ precursors (SOPs) in *Drosophila* generates distinct cell types of the mature sensory organ. The fate of the daughter cells (pIIa and pIIb) that arise following SOP cell division is enforced by asymmetric Delta-to-Notch signalling, in which Delta on the pIIb cell signals to Notch on the pIIa cell. Following SOP cell division, only the pIIb cell receives the Rab11-binding protein FIP3/Nuf and is able to produce pericentrosomal Rab11-positive REs (Emery et al., 2005). These appear to be required for the recycling of the Notch receptor ligand

Delta to the cell surface of pIIb cells and the consequent ability of Delta to stimulate Notch at the pIIa cell surface (Emery et al., 2005). RE can thus regulate signalling pathways and influence the developmental fate of individual cells. This idea is underscored by the observation that mutations in Sec15 produce a phenotype consistent with a loss of Notch signalling (Jafar-Nejad et al., 2005). The asymmetric segregation of FIP3/Nuf may allow the pIIb cell to use the Rab11-Sec15 machinery differently from the pIIa cell and thereby take on the role of the Delta-signal-sending cell.

The future

A mutation in Sec15l1 and a consequent defect in transferrin recycling from Rab11-positive REs causes anaemia in haemoglobin-deficient mice (Lim et al., 2005). REs also coordinate the directed secretion of newly synthesized tumour necrosis factor α with the supply of membrane to the expanding phagocytic cup in activated macrophages (Murray et al., 2005). Furthermore, they supply AMPA receptors for long-term potentiation, providing a mechanistic link between synaptic potentiation and membrane remodelling during synapse modification (Park et al., 2004). REs also regulate adhesion molecule recycling during leukocyte chemotaxis (Fabbri et al., 2005), which is consistent with earlier observations of polarised vesicle recycling during cell migration (Hopkins et al., 1994). REs are thus deeply involved in targeting membrane components from the endocytic and biosynthetic pathways to regions of the cell surface subject to dynamic membrane and cytoskeletal reorganisation. The association of Rab11, RalA and Arf6 with REs and their individual interactions with exocyst components suggest there is an intimate relationship between RE-controlled membrane trafficking and cortical cytoskeletal remodelling. Understanding how this is coordinated in the various interdependent cellular processes described is now an important goal in the field of membrane trafficking.

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